CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

FINAL PRINTED LABELING

PRODUCT INFORMATION

REBETRON™
Combination Therapy
containing
REBETOL® (ribavirin, USP) Capsules
and
INTRON® A (interferon alfa-2b, recombinant) Injection

Combination REBETOL/INTRON A therapy is contraindicated in women who are pregnant. Women of childbearing potential and men must use effective contraception during treatment and during the 6-month posttreatment follow-up period. Significant teratogenic and/or embryocidal potential has been demonstrated for ribavirin in all animal species studied. See CONTRAINDICATIONS.

DESCRIPTION

INTRON® A

INTRON A is Schering Corporation's brand name for interferon alfa-2b, recombinant, a purified sterile recombinant interferon product.

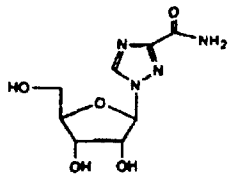
Interferon alfa-2b, recombinant has been classified as an alpha interferon and is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The fermentation is carried out in a defined nutrient medium containing the antibiotic tetracycline hydrochloride at a concentration of 5 to 10 mg/L; the presence of this antibiotic is not detectable in the final product.

INTRON A Injection is a clear, colorless solution. The 3 million IU vial of INTRON A Injection contains 3 million IU of interferon alfa-2b, recombinant per 0.5 mL. The 18 million IU multidose vial of INTRON A Injection contains a total of 22.8 million IU of interferon alfa-2b, recombinant per 3.8 mL (3 million IU/0.5 mL) in order to provide the delivery of six 0.5 mL doses, each containing 3 million IU of INTRON A (for a label strength of 18 million IU). The 18 million IU INTRON A Injection multidose pen contains a total of 22.5 million IU of interferon alfa-2b, recombinant per 1.5 mL (3 million IU/0.2 mL) in order to provide the delivery of six 0.2 mL doses, each containing 3 million IU of INTRON A (for a label strength of 18 million IU). Each mL also contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg m-cresol as a preservative.

Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay, the corresponding quantities of interferon alfa-2b, recombinant in the vials and pen described above are approximately 0.012 mg, 0.088 mg, and 0.087 mg protein, respectively.

REBETOL®

REBETOL is Schering Corporation's brand name for ribavirin, a nucleoside analog with antiviral activity. The chemical name of ribavirin is 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

REBETOL Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.

Mechanism of Action

Interferon alfa-2b, recombinant/Ribavirin The mechanism of inhibition of hepatitis C virus (HCV) RNA by combination therapy with INTRON A and REBETOL has not been established.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Interferon alfa-2b, recombinant Single and multiple dose pharmacokinetic properties of INTRON A are summarized in **TABLE 1**. Following a single 3 million IU (MIU) subcutaneous dose in 12 patients with chronic hepatitis C, mean (% CV*) serum concentrations peaked at 7 (44%) hours. Following 4 weeks of subcutaneous dosing with 3 MIU three times a week (TIW), interferon serum concentrations were undetectable predose. However, a twofold increase in bioavailability was noted upon multiple dosing of interferon; the reason for this is unknown. Mean half-life values following single and multiple dose administrations were 6.8 (24%) hours and 6.5 (29%) hours, respectively.

Ribavirin Single- and multiple-dose pharmacokinetic properties in adults with chronic hepatitis C are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400-600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Food on Absorption of Ribavirin Both AUC_{tf} and C_{max} increased by 70% when REBETOL was administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies were conducted without instructions with respect to food consumption. (See **DOSAGE AND ADMINISTRATION**.)

Effect of Antacid on Absorption of Ribavirin Coadministration with an antacid containing magnesium, aluminum, and simethicone (Mylanta®) resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for INTRON A and REBETOL When Administered Individually to Adults with Chronic Hepatitis C

Parameter	INTRON A (N=12)		REBETOL (N=12)	
	Single Dose 3 MIU	Multiple Dose 3 MIU TIW	Single Dose 600 mg	Multiple Dose 600 mg BID
T_{max} (hr)	7 (44)	5 (37)	1.7 (46) ***	3 (60)
C_{max} *	13.9 (32)	29.7 (33)	782 (37)	3680 (85)
AUC_{tf} **	142 (43)	333 (39)	13400 (48)	228000 (25)
$T_{1/2}$ (hr)	6.8 (24)	6.5 (29)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)			2825 (9)†	
Apparent Clearance (L/hr)	14.3 (17)		38.2 (40)	
Absolute Bioavailability			64% (44)††	

* IU/mL for INTRON A and ng/mL for REBETOL

** IU.hr/mL for INTRON A and ng.hr/mL for REBETOL

† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5
†† N = 6
††† N = 11

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_t-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A and REBETOL Capsules in a multiple-dose pharmacokinetic study.

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to subjects with varying degrees of renal dysfunction. The mean AUC_{ss} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). This appears to be due to reduction of apparent clearance in these patients. Ribavirin was not removed by hemodialysis. REBETOL is not recomended for patients with severe renal impairment (see **WARNINGS**).
Hepatic Dysfunction The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{ss} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C), when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.
Pediatric Patients Pharmacokinetic evaluations for pediatric subjects have not been performed.
Elderly Patients Pharmacokinetic evaluations for elderly subjects have not been performed.
Gender There were no clinically significant pharmacokinetic differences noted in a single-dose study of eighteen male and eighteen female subjects.

* ***In this section of the label, numbers in parenthesis indicate % coefficient of variation.***

INDICATIONS AND USAGE

The combination therapy of REBETOL (ribavirin, USP) Capsules with INTRON A (interferon alfa-2b, recombinant) Injection is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy.

Description of Clinical Studies

Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive REBETOL 1200 mg/day (1000 mg/day for patients weighing ≤75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled and treated 153 patients who, at baseline, were 67% male, 92% caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in Europe, Israel,

Canada, and Australia, enrolled and treated 192 patients (64% male, 95% caucasian, mean Knodell score 6.6, and 56% genotype 1).

Study results are summarized in TABLE 2.

TABLE 2. Patients with Virologic and Histologic Responses*

	US Study		International Study	
	INTRON A plus REBETOL N=77	INTRON A plus Placebo N=76	INTRON A plus REBETOL N=96	INTRON A plus Placebo N=96
Virological Response				
-Responder[1]	33(43)	3(4)	46(48)	5(5)
-Nonresponder	36(47)	66(87)	45(47)	91(95)
-Missing	8(10)	7(9)	5(5)	0(0)
Histological Response				
-Improvement[2]	38(49)	27(36)	49(51)	30(31)
-No improvement	23(30)	37(49)	29(30)	44(46)
-Missing	16(21)	12(16)	18(19)	22(23)

* Number (%) of Patients.

1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) - pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Virologic and histologic response rates to therapy were similar in both male and female patients.

CONTRAINDICATIONS

Combination REBETOL/INTRON A therapy must not be used by women who are or may become pregnant. Combination REBETOL/INTRON A therapy should not be initiated until a report of a negative pregnancy test has been obtained. Women of childbearing potential and men must use effective contraception during treatment and during the 6-month posttreatment follow-up period. Significant teratogenic and/or embryocidal potential has been demonstrated for ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of REBETOL. If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, physicians are encouraged to report such cases by calling (800) 727-7064.

REBETOL Capsules in combination with INTRON A Injection is contraindicated in patients with a history of hypersensitivity to alpha interferons and/or ribavirin or any component of the injection and/or capsule.

Patients with autoimmune hepatitis must not be treated with combination REBETOL/INTRON A therapy.

WARNINGS

Anemia

ANEMIA (HEMOGLOBIN <10 G/DL) WAS OBSERVED IN 10% OF REBETOL/INTRON A-TREATED PATIENTS IN CLINICAL TRIALS (SEE ADVERSE REACTIONS LABORATORY VALUES - *HEMOGLOBIN*). ANEMIA OCCURRED WITHIN 1 - 2 WEEKS OF INITIATION OF RIBAVIRIN THERAPY. BECAUSE OF THIS INITIAL ACUTE DROP IN HEMOGLOBIN, IT IS ADVISED THAT COMPLETE BLOOD COUNTS (CBC) SHOULD BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY OR MORE FREQUENTLY IF CLINICALLY INDICATED. PATIENTS SHOULD THEN BE FOLLOWED AS CLINICALLY APPROPRIATE.

The anemia associated with REBETOL/INTRON A therapy may result in deterioration of cardiac function and/or exacerbation of the symptoms of coronary disease. Patients should be assessed before initiation of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See DOSAGE AND ADMINISTRATION.) Because

cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use combination REBETOL/INTRON A therapy. (See ADVERSE REACTIONS.)

Similarly, patients with hemoglobinopathies (eg, thalassemia, sickle-cell anemia) should not be treated with combination REBETOL/INTRON A therapy.

Psychiatric

SEVERE PSYCHIATRIC ADVERSE EVENTS, INCLUDING DEPRESSION AND SUICIDAL BEHAVIOR (SUICIDAL IDEATION, SUICIDAL ATTEMPTS, AND SUICIDES) HAVE OCCURRED DURING COMBINATION REBETOL/INTRON A THERAPY AND WITH INTERFERON ALPHA MONOTHERAPY, BOTH IN PATIENTS WITH AND WITHOUT A PREVIOUS PSYCHIATRIC ILLNESS. REBETOL/INTRON A therapy should be used with extreme caution in patients with a history of pre-existing psychiatric disorders who report a history of severe depression, and physicians should monitor all patients for evidence of depression. In severe cases, therapy should be stopped and psychiatric intervention sought. In general, the adverse events resolve on cessation of therapy; however, adjunctive psychiatric medications may be required. (See ADVERSE REACTIONS.)

Pulmonary

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, including fatality, have been reported during therapy with REBETOL/INTRON A. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and, if appropriate, combination REBETOL/INTRON A treatment should be discontinued.

Other

- Combination REBETOL/INTRON A therapy should be used with caution in patients with creatinine clearance <50 mL/min.
- Diabetes mellitus and hyperglycemia have been observed in patients treated with INTRON A.
- Ophthalmologic disorders have been reported with treatment with alpha interferons. Investigators using alpha interferons have reported the occurrence of retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction in rare instances. Any patient complaining of loss of visual acuity or visual field should have an eye examination. Because these ocular events may occur in conjunction with other disease states, a visual exam prior to initiation of combination REBETOL/INTRON A therapy is recommended in patients with diabetes mellitus or hypertension.
- Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed in INTRON A-treated patients; if such an acute reaction develops, combination REBETOL/INTRON A therapy should be discontinued immediately and appropriate medical therapy instituted.
- Combination REBETOL/INTRON A therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be controlled by medication.

PRECAUTIONS

Exacerbation of autoimmune disease has been reported in patients receiving alpha interferon therapy. REBETOL/INTRON A therapy should be used with caution in patients with other autoimmune disorders.

There have been reports of interferon, including INTRON A, exacerbating pre-existing psoriasis; therefore, combination REBETOL/INTRON A therapy should be used in these patients only if the potential benefit justifies the potential risk.

The safety and efficacy of REBETOL/INTRON A therapy has not been established in organ transplant patients, decompensated hepatitis C patients, patients who are nonresponders or naive to interferon therapy, or patients coinfected with HBV or HIV.

REBETOL monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication.

Information for Patients Combination REBETOL/INTRON A therapy should not be initiated until a report of a negative pregnancy test has been obtained. It is also recommended that the patient be advised of the need to perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of adequate contraception prior to initiating therapy. Patients (male and female) should be advised to practice adequate contraception during combination REBETOL/INTRON A therapy and should be advised to notify the physician in the event of a pregnancy.

(See **CONTRAINDICATIONS.**)

If pregnancy does occur during treatment or during 6 months posttherapy, the patient must be advised of the significant teratogenic risk of REBETOL therapy to the fetus. Patients, or partners of patients, should report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician immediately. Physicians are encouraged to report such cases by calling (800) 727-7064.

Patients receiving combination REBETOL/INTRON A treatment should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the **MEDICATION GUIDE.** There are no data evaluating whether REBETOL/INTRON A therapy will prevent transmission of infection to others.

If home use is prescribed, a puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

The most common adverse experiences occurring with combination REBETOL/INTRON A therapy are "flu-like" symptoms, such as headache, fatigue, myalgia, and fever (see **ADVERSE REACTIONS**) and appear to decrease in severity as treatment continues. Some of these "flu-like" symptoms may be minimized by bedtime administration of INTRON A therapy. Antipyretics should be considered to prevent or partially alleviate the fever and headache. Another common adverse experience associated with INTRON A therapy is thinning of the hair.

Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter (see **Laboratory Tests**). It is advised that patients be well hydrated, especially during the initial stages of treatment.

Laboratory Tests The following laboratory tests are recommended for all patients on combination REBETOL/INTRON A therapy, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and differential white blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.

Carcinogenesis and Mutagenesis Carcinogenicity studies with interferon alfa-2b, recombinant have not been performed because neutralizing activity appears in the serum after multiple dosing in all of the animal species tested.

Adequate studies to assess the carcinogenic potential of ribavirin in animals have not been conducted. However, ribavirin is a nucleoside analog that has produced positive findings in multiple *in vitro* and animal *in vivo* genotoxicity assays, and should be considered a potential carcinogen. Further studies to assess the carcinogenic potential of ribavirin in animals are ongoing.

Mutagenicity studies have demonstrated that interferon alfa-2b, recombinant is not mutagenic. Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67 - 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 - 1X the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility No reproductive toxicology studies have been performed using interferon alfa-2b, recombinant in combination with ribavirin. However, evidence provided below for interferon alfa-2b, recombinant and ribavirin when administered alone indicate that both agents have adverse effects on reproduction. It should be assumed that the effects produced by either agent alone will also be caused by the combination of the two agents. Interferons may impair human fertility. In studies of interferon alfa-2b recombinant administration in nonhuman primates, menstrual cycle abnormalities have been observed. Decreases in serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon. In addition, ribavirin demonstrated significant embryotoxic and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women should not receive combination REBETOL/INTRON A therapy unless they are using effective contraception during the therapy period. Based on a multiple dose $t_{1/2}$ of ribavirin of 12 days, effective contraception should be utilized for 6 months posttherapy (eg, 15 half-lives of clearance for ribavirin).

Combination REBETOL/INTRON A therapy should be used with caution in fertile men. In a study in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 35 to 150 mg/kg/day (estimated human equivalent of 2.92 - 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.2 - 0.8 X the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles. A follow-up study to further assess these findings is ongoing.

Animal Toxicology Long-term studies in the mouse and rat (18 - 24 months; doses of 20 - 75 and 10 - 40 mg/kg/day, respectively (estimated human equivalent doses of 1.67 - 6.25 and 1.43 - 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 - 0.4 X the maximum human 24-hour dose of ribavirin)) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

Pregnancy Category X (see CONTRAINDICATIONS) Interferon alfa-2b, recombinant has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60 kg adult). There are no adequate and well-controlled studies in pregnant women.

Ribavirin produced significant embryotoxic and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 X the recommended human 24-hour dose of ribavirin). No maternal toxicity nor effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 X the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 - 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 X the maximum recommeded human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin exposure to the fetus, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

It is advised that male patients be counseled to practice effective contraception during treatment with combination REBETOL/INTRON A therapy and for the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

Women of childbearing potential should not receive combination REBETOL/INTRON A therapy unless they are using effective contraception during the therapy period. In addition, effective contraception should be utilized for 6 months posttherapy based on a multiple dose $t_{1/2}$ of ribavirin of 12 days.

If pregnancy occurs in a patient or partner of a patient during treatment or during the 6 months after treatment cessation, physicians are encouraged to report such cases by calling (800) 727-7064.

Nursing Mothers It is not known whether REBETOL and INTRON A are excreted in human milk. However, studies in mice have shown that mouse interferons are excreted into the milk. Because of the potential for serious adverse reactions from the drugs in nursing infants, a decision should be made whether to discontinue nursing or to discontinue combination REBETOL/INTRON A therapy, taking into account the importance of the therapy to the mother.

Pediatric Use Safety and effectiveness in pediatric patients below the age of 18 years have not been established. (See **INDICATIONS AND USAGE.**)

ADVERSE REACTIONS

The safety of combination REBETOL/INTRON A therapy was evaluated in controlled trials of 173 HCV-infected patients who had relapsed after interferon therapy. (See *Description of Clinical Studies.*) Overall, 6% of patients discontinued therapy due to adverse events in the combination arm compared to 3% in the interferon arm.

The primary toxicity of ribavirin is anemia. Reductions in hemoglobin levels occured within the first 1-2 weeks of therapy (see **WARNINGS**). Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients treated with REBETOL/INTRON A. (See **WARNINGS.**)

Psychiatric events, most commonly insomnia, depression, and irritablility occurred in 53% (91/173) of patients. Suicidal behavior (ideation, attempts, and suicides) occurred in < 1% of patients. (See **WARNINGS.**)

Selected treatment-emergent adverse events that occurred with ≥5% incidence are provided in **TABLE 3** by treatment group.

TABLE 3. Selected Treatment-Emergent Adverse Events: Treated Relapse Patients

	Percentage of Patients			
	US Study		International Study	
Patients Reporting Adverse Events	INTRON A plus REBETOL N=77	INTRON A plus Placebo N=76	INTRON A plus REBETOL N=96	INTRON A plus Placebo N=96
Application Site Disorders				
injection site inflammation	6	8	5	4
injection site reaction	5	3	0	3
Body as a Whole - General Disorders				
headache	66	68	47	43
fatigue	60	53	35	28
rigors	43	37	13	8
fever	32	36	31	30
influenza-like symptoms	13	13	29	32
asthenia	10	4	27	26
chest pain	6	7	1	5
Central & Peripheral Nervous System Disorders				
dizziness	26	21	9	5
Gastrointestinal System Disorders				
nausea	47	33	25	9
anorexia	21	14	19	11
dyspepsia	16	9	6	8
vomiting	12	8	6	1
Musculoskeletal System Disorders				
myalgia	61	58	30	24
arthralgia	29	29	15	18
musculo-skeletal pain	22	28	18	18
Psychiatric Disorders				
insomnia	26	25	16	21
irritability	25	20	8	10
depression	23	14	10	8
emotional lability	12	8	7	3
concentration impaired	10	12	4	2
nervousness	5	4	7	1

Respiratory System Disorders				
dyspnea	17	12	11	1
sinusitis	12	7	3	1
Skin and Appendages Disorders				
alopecia	27	26	17	11
rash	21	5	6	4
pruritus	13	4	13	8
Special Senses, Other Disorders				
taste perversion	6	5	9	2

* Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during combination REBETOL/INTRON A treatment are described below (see **TABLE 4**).

Hemoglobin Hemoglobin decreases among patients on combination therapy began at Week 1, with stabilization by Week 4. The mean maximum decrease from baseline was 2.8 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to pretreatment levels within 4 - 8 weeks of cessation of therapy in most patients.

Neutrophils There were decreases in neutrophil counts in both the combination REBETOL/INTRON A and INTRON A plus placebo dose groups. The mean maximum decrease in neutrophil count in the US study was 1.3×10^9/L and in the International study was 1.6×10^9/L. Neutrophil counts returned to pretreatment levels within 4 weeks of cessation of therapy in most patients.

Platelets Mean platelet values remained in the normal range of $150 - 450 \times 10^9$/L during combination REBETOL/INTRON A and INTRON A plus placebo therapy; however, mean platelet values were approximately 10% lower in the INTRON A plus placebo group than the REBETOL/INTRON A group. Mean platelet values returned to baseline levels within 4 weeks after treatment discontinuation.

Thyroid Function Of patients who entered the studies without thyroid abnormalities, approximately 1% to 2% developed thyroid abnormalities requiring clinical intervention.

Bilirubin and Uric Acid Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurs most frequently in patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

TABLE 4. Selected Hematologic Values During Treatment with REBETOL plus INTRON A

	Percentage of Patients			
	US Study		International Study	
	INTRON A plus REBETOL N=77	INTRON A plus PLACEBO N=76	INTRON A plus REBETOL N=95	INTRON A plus PLACEBO N=96
Hemoglobin (g/dL)				
9.5-10.9	21	3	24	1
8.0-9.4	4	0	1	0
6.5-7.9	0	0	0	0
<6.5	0	0	0	0
Leukocytes x 10^9/L				
2.0-2.9	45	26	34	6
1.5-1.9	5	3	2	1
1.0-1.4	0	0	0	0
<1.0	0	0	0	0
Neutrophils x 10^9/L				
1.0-1.49	42	34	32	31
0.75-0.99	16	18	12	6
0.5-0.74	8	4	6	0
<0.5	5	8	0	2
Platelets x 10^9/L				
70-99	6	12	6	6
50-69	0	5	1	3
<49	0	0	0	0

Total Bilirubin (mg/dL)				
1.5-3.0	21	7	13	3
3.1-6.0	3	0	3	0
6.1-12.0	0	0	0	0
>12.0	0	0	0	0

OVERDOSAGE

In combination REBETOL/INTRON A clinical trials, the maximum overdose reported was a dose of 39 million units of INTRON A (13 subcutaneous injections of 3 million IU each) taken with 10 g of REBETOL (fifty 200-mg capsules) in an investigator-initiated trial. The patient was observed for 2 days in the emergency room during which time no adverse event from the overdose was noted.

DOSAGE AND ADMINISTRATION

INTRON A Injection should be administered subcutaneously and REBETOL Capsules should be administered orally (see TABLE 5).

The recommended dose of REBETOL depends on the patient's body weight. The recommended doses of REBETOL and INTRON A are given in TABLE 5 and should be administered for a period of 6 months (24 weeks). The safety and efficacy of the combination of REBETOL and INTRON A therapy has not been established beyond 6 months of treatment.

TABLE 5. Recommended Dosing

Body weight	REBETOL Capsules	INTRON A Injection
≤ 75 kg	2 x 200 mg capsules AM, 3 x 200 mg capsules PM p.o.	3 million IU 3 times weekly s.c.
> 75 kg	3 x 200 mg capsules AM, 3 x 200 mg capsules PM p.o.	3 million IU 3 times weekly s.c.

REBETOL may be administered without regard to food. (See CLINICAL PHARMACOLOGY.)

Variations in dosage, routes of administration, and adverse reactions exist among different brands of interferon. There is no information regarding the use of REBETOL Capsules with other interferons.

Dose Modifications (TABLE 6)

If severe adverse reactions or laboratory abnormalities develop during combination REBETOL/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, REBETOL/INTRON A therapy should be discontinued.

REBETOL/INTRON A therapy should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See WARNINGS.)

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination REBETOL/INTRON A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her REBETOL dose reduced to 600 mg daily (1 x 200 mg capsule AM, 2 x 200 mg capsules PM). A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from REBETOL/INTRON A therapy. (See WARNINGS.)

It is recommended that a patient who experiences moderate depression (persistent low mood, loss of interest, poor self image, and/or hopelessness) have his/her INTRON A dose temporarily reduced and/or be considered for medical therapy. A patient experiencing severe depression or suicidal ideation/attempt should be discontinued from REBETOL/INTRON A therapy and followed closely with appropriate medical management. (See WARNINGS.)

TABLE 6. Guidelines for Dose Modifications

	Dose Reduction* REBETOL - 600 mg daily INTRON A - 1.5 million IU TIW	Permanent Discontinuation of Treatment REBETOL and INTRON A
Hemoglobin	<10 g/dL (REBETOL)	<8.5 g/dL
	Cardiac History Patients only. ≥2 g/dL decrease during any 4-week period during treatment (REBETOL/INTRON A)	**Cardiac History Patients only. <12 g/dL after 4 weeks of dose reduction**
White blood count	$<1.5 \times 10^9$/L (INTRON A)	$<1.0 \times 10^9$/L
Neutrophil count	$<0.75 \times 10^9$/L (INTRON A)	$<0.5 \times 10^9$/L
Platelet count	$<50 \times 10^9$/L (INTRON A)	$<25 \times 10^9$/L

*Study medication to be dose reduced is shown in parenthesis

Administration of INTRON A Injection

At the discretion of the physician, the patient may self-administer the INTRON A. (See illustrated **MEDICATION GUIDE** for instructions.)

The Intron A Injection is supplied as a clear and colorless solution. The appropriate INTRON A dose should be withdrawn from the vial or set on the multidose pen and injected subcutaneously. After administration of INTRON A Injection, it is essential to follow the procedure for proper disposal of syringes and needles. (See **MEDICATION GUIDE** for detailed instructions.)

Vial/Pen Label Strength	Fill Volume	Concentration
3 million IU vial	0.5 mL	3 million IU/0.5 mL
18 million IU multidose vial†	3.8 mL	3 million IU/0.5 mL
18 million IU Mulitdose Pen††	1.5 mL	3 million IU/0.2 mL

†This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b, recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing 3 million IU of INTRON A (for a label strength of 18 million IU).
†† This is a multidose pen which contains a total of 22.5 million IU of interferon alfa-2b, recombinant per 1.5 mL in order to provide the delivery of six 0.2-mL doses, each containing 3 million IU of INTRON A (for a label strength of 18 million IU).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. INTRON A Injection may be administered using either sterilized glass or plastic disposable syringes.
Stability INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and at 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable at 30°C (86°F) for up to 2 days. The solution is clear and colorless.

HOW SUPPLIED

REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in blisters.

INTRON A Injection is a clear, colorless solution packaged in single dose and multidose vials, and a multidose pen.

INTRON A Injection and REBETOL Capsules are available in the following combination package

presentations:

	Each REBETRON Combination Package Consists of:	
For Patients ≤75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial) and 6 syringes and alchohol swabs. Two boxes containing 35 REBETOL Capsules each for a total of 70 capsules (5 capsules per blister card).	(NDC 0085-1241-02)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL) and 6 syringes and alchohol swabs. Two boxes containing 35 REBETOL Capsules each for a total of 70 capsules (5 capsules per blister card).	(NDC 0085-1236-02)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL) and 6 disposable needles and alcohol swabs. Two boxes containing 35 REBETOL Capsules each for a total of 70 capsules (5 capsules per blister card).	(NDC 0085-1258-02)
For Patients >75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial) and 6 syringes and alchohol swabs. Two boxes containing 42 REBETOL Capsules each for a total of 84 capsules (6 capsules per blister card).	(NDC 0085-1241-01)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL) and 6 syringes and alchohol swabs. Two boxes containing 42 REBETOL Capsules each for a total of 84 capsules (6 capsules per blister card).	(NDC 0085-1236-01)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL) and 6 disposable needles and alcohol swabs. Two boxes containing 42 REBETOL Capsules each for a total of 84 capsules (6 capsules per blister card).	(NDC 0085-1258-01)
For REBETOL Dose Reduction	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial) and 6 syringes and alchohol swabs. One box containing 42 REBETOL Capsules (6 capsules per blister card).	(NDC 0085-1241-03)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL) and 6 syringes and alchohol swabs. One box containing 42 REBETOL Capsules (6 capsules per blister card).	(NDC 0085-1236-03)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL) and 6 disposable needles and alcohol swabs. One box containing 42 REBETOL Capsules (6 capsules per blister card).	(NDC 0085-1258-03)

Storage Conditions

Store the REBETOL Capsules plus INTRON A Injection combination package refrigerated between 2°C and 8°C (36° and 46° F).

When separated, the individual carton of REBETOL Capsules should be stored refrigerated between 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions are permitted between 15° and 30°C (59° and 86°F).

When separated, the individual carton or vial of INTRON A Injection and the INTRON A Multidose Pen should be stored refrigerated between 2° and 8°C (36° and 46°F).

Schering Corporation
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U.S. Patents 4,530,901 & 4,211,771

B-21617601

REBETRON™
Combination Therapy
containing
REBETOL®
(ribavirin, USP) Capsules
and
INTRON® A
(interferon alfa-2b, recombinant)
Injection

IMPORTANT PATIENT INFORMATION

Please read this information carefully before you begin taking your combination REBETOL/INTRON A therapy. It is important to read this each time your prescription is refilled in case new information becomes available. This summary does not tell you everything about combination REBETOL/INTRON A therapy. Your doctor is the best source of information about these medicines. You should talk with him or her before starting therapy and at your regular check-ups. You may also ask your doctor or pharmacist for a copy of a longer leaflet about this therapy that is written for health professionals.

What is the most important information I should know about combination REBETOL/INTRON A therapy?

1. **COMBINATION REBETOL/INTRON A THERAPY COULD SERIOUSLY HARM YOUR UNBORN CHILD**

- **If you or your partner are pregnant, you should not receive combination REBETOL/INTRON A therapy.**
- **Pregnancy should not be planned while you or your partner are on therapy or for 6 months after therapy.**

- **If you or your partner become pregnant while on therapy or during the 6 months after stopping therapy, consult your physician immediately.**
- If you are a woman of childbearing age YOU MUST HAVE A NEGATIVE PREGNANCY TEST BEFORE TREATMENT, and a pregnancy test each month during treatment. BOTH MALE AND FEMALE PATIENTS MUST USE EFFECTIVE CONTRACEPTION during treatment and for the 6 months after treatment is completed. You should discuss with your doctor how you or your partner can prevent getting pregnant.

2. **REBETOL causes anemia, which is a decrease in the number of red blood cells you have. This can be dangerous, especially for patients who already have heart or circulatory (cardiovascular) problems. Talk with your doctor before taking combination REBETOL/INTRON A therapy if you have or have ever had any cardiovascular problems.**
3. Combination REBETOL/INTRON A therapy should be used only by patients who have had their hepatitis C infections return after having been successfully treated with interferon alone.

What is combination REBETOL/INTRON A therapy?

REBETRON combination therapy consists of two separate medications, REBETOL Capsules (ribavirin) and INTRON A Injection (interferon). REBETOL is an antiviral agent (fights infection), but does not work when used by itself to treat chronic hepatitis C. INTRON A generally helps the body's immune system to fight infections. It is not known exactly how the combined products work together to fight the hepatitis C infection.

This combination of medicines is used to treat hepatitis C infection in patients who previously received interferon treatment alone but whose infection then returned.

Combination REBETOL/INTRON A therapy may reduce the amount of hepatitis C virus in the blood stream to below the level that can be measured by a laboratory test.

It is not yet known if combination REBETOL/INTRON A therapy will cure hepatitis C or prevent the cirrhosis, liver failure, or liver cancer that can result from being infected with the hepatitis C virus.

It is also unknown if combination REBETOL/INTRON A therapy will prevent one infected person from infecting another person with hepatitis C.

Who should not take combination REBETOL/INTRON A therapy?

DO NOT USE these medicines:

- **IF YOU OR YOUR PARTNER ARE PREGNANT.**
- **IF YOU OR YOUR PARTNER PLAN TO BECOME PREGNANT DURING TREATMENT OR DURING THE 6 MONTHS AFTER TREATMENT.**
- **IF YOU OR YOUR PARTNER BECOME PREGNANT DURING TREATMENT. Combination REBETOL/INTRON A therapy can cause serious harm to your unborn child. Therefore, both you and your partner MUST USE EFFECTIVE CONTRACEPTION during this time.**
- If you are allergic to any of the ingredients in REBETOL Capsules or INTRON A Injection or to any alpha interferon.
- If you have autoimmune hepatitis (hepatitis caused by cells in your body attacking each other).

If you have any of the following medical conditions or other serious medical problems, you should discuss these with your doctor before taking this medicine:

- High blood pressure, heart attack, or other heart problems, because combination therapy may cause heart problems to become worse.
- Blood disorders; including anemia (low red blood cell count), thalassemia (Mediterranean anemia), and sickle-cell anemia, because combination therapy may further reduce the number of red blood cells you have. This may make you feel dizzy or weak and could worsen any heart problems you might have.
- Kidney problems.
- Liver problems (except hepatitis C infection).
- Nervous or mental problems (such as depression, anxiety etc.), because the combination could make these problems worse.
- Body organ transplant and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system).
- Thyroid disease.
- Cancer.
- Infection with Hepatitis B Virus and/or Human Immunodeficiency Virus (the virus that causes AIDS.).
- Diabetes.

- Previously untreated for hepatitis C.
- Previously failed interferon therapy for hepatitis C.

How should I take combination REBETOL/INTRON A therapy?

Your doctor has determined the correct dose of REBETOL based on your weight. Your doctor may adjust your dose of REBETOL and/or INTRON A according to your response to these medicines. Routine blood tests will help your doctor to monitor your response to treatment. The recommended doses of INTRON A Injection and REBETOL Capsules are shown in the table below:

If your weight is	Take this many REBETOL Capsules each day:	Inject this amount of INTRON A under your skin (subcutaneously):
165 pounds or less	2 capsules in the AM 3 capsules in the PM	3 million international units 3 times per week
More than 165 pounds	3 capsules in the AM 3 capsules in the PM	3 million international units 3 times per week

Your doctor may recommend a lower dose of REBETOL or INTRON A if you have certain adverse events.

You can take your REBETOL with or without food, but it is best to take it the same way every day.

It is important to follow your dosing schedule and your doctor's instructions on how to take your medications. Take the medicine for as long as prescribed and do not exceed the recommended dosage. If you miss a dose of REBETOL, take the missed dose as soon as possible during the same day. If an entire day has gone by, check with your doctor about what to do. Do not double the next dose. If you miss a dose of INTRON A, take the missed dose as soon as possible during the same day or on the next day, and continue the dosing schedule provided to you by your doctor. If several days go by, check with your doctor about

what to do. Do not double the next dose. Instructions on how to inject your INTRON A dose are provided later in this medication guide.

What should I avoid while taking combination REBETOL/INTRON A therapy?

- **YOU OR YOUR PARTNER SHOULD AVOID BECOMING PREGNANT while taking combination REBETOL/INTRON A therapy and for 6 months after stopping therapy. Combination REBETOL/ INTRON A therapy can cause serious harm to your unborn child. Thus, you MUST USE EFFECTIVE CONTRACEPTION during this time. If you or your partner become pregnant during treatment or during the 6 months after treatment you should immediately report the pregnancy to your doctor. Your doctor should call (800) 727-7064.**
- You should not inject yourself with any medicine that appears discolored or irregular.
- Tell your doctor about any other medications you are taking.
- Ask your doctor if there are other things you should avoid.

Medicines are sometimes prescribed for purposes other than those listed in this medication guide. Remember, this medicine is for you and must be used as prescribed by your doctor. Never give it to anyone else.

What are the possible side effects of combination REBETOL/INTRON A therapy?

- **REBETOL causes a reduction in the number of red blood cells you have which can be dangerous, especially if you have heart or circulatory problems. It is very important that your doctor check your red blood cell count before starting therapy and at least two more times during the first four weeks of therapy. If needed your doctor will check your blood counts more often while you are receiving therapy. IT IS IMPORTANT TO HAVE YOUR RED BLOOD CELL COUNT CHECKED MORE OFTEN IF YOU HAVE ANY HEART PROBLEMS OR HIGH BLOOD PRESSURE.**
- Most patients who take combination REBETOL/INTRON A therapy have "flu-like" symptoms that usually diminish after the first few weeks of therapy. These include headache, fatigue, muscle ache, and fever. You can minimize some of these "flu-like" symptoms by injecting your INTRON A at bedtime. Over-the-counter pain and fever reducers, such as acetaminophen or ibuprofen, can be used to prevent or partially relieve the fever and headache.

- Some patients experience emotional or behavioral problems such as irritability (getting easily excited), and/or depression (feeling low, feeling bad about yourself, and/or feeling hopeless).
- **A few patients have very serious psychological problems including thoughts about killing themselves and have committed suicide. These side effects have been associated with interferon therapy alone and with combination REBETOL/INTRON A therapy. In general, these events and behaviors stop after therapy is stopped. IF YOU EXPERIENCE ANY OF THESE THOUGHTS OR FEELINGS YOU SHOULD TELL YOUR DOCTOR IMMEDIATELY.**
- Some patients experience insomnia (not being able to sleep).
- Hair thinning is a common event which occurs in the later stages of treatment. Hair loss stops and hair growth returns after therapy is stopped.
- You may get a rash during therapy. Your doctor can recommend treatment to deal with the rash if this occurs.
- If you have psoriasis, it may get worse during treatment because of INTRON A's effects on your immune system.
- TELL YOUR DOCTOR IMMEDIATELY IF YOU FEEL DEPRESSED, HAVE CHEST PAIN, or SHORTNESS OF BREATH.
- Like all medicines, combination REBETOL/INTRON A therapy can cause a number of side effects. This summary does not include all possible side effects of combination therapy. Your doctor has been informed of other complaints reported during clinical trials. It is important to talk with your doctor about possible side effects. If you want to read more, ask your doctor or pharmacist to give you the professional labeling.

What should I know about the hepatitis C virus?

Hepatitis C is a viral disease that causes inflammation of the liver. It develops into a chronic continuing condition in a great majority of patients. Patients with chronic hepatitis C may develop cirrhosis, liver cancer, or possibly even liver failure. Liver failure due to hepatitis C is currently the leading cause of liver transplants in the United States. Combination therapy may reduce hepatitis C virus in your blood stream to levels that cannot be measured by laboratory tests. However, it is not yet proven if it will cure your disease or prevent the complications associated with infection.

How do I inject INTRON A?

- DO NOT INJECT INTRON A UNTIL YOUR DOCTOR HAS THOROUGHLY TRAINED YOU IN THE PROPER TECHNIQUES.

- If you have any questions, contact your doctor prior to injecting INTRON A.
- Use the sterile technique as instructed by your doctor. Destroy disposable syringes and needles after each use and discard appropriately according to directions provided by your doctor or nurse.
- If your injection is given by another individual, he or she should be instructed by the doctor on the use of sterile technique and how to avoid an accidental needle stick.

PREPARING THE INTRON A DOSE

IMPORTANT: Before each use, the liquid in the vial should be clear, colorless to light yellow, and without particles. Do not use if you see particles or the color is not correct; call your doctor, nurse, or pharmacist.

1. Wash your hands thoroughly and remove the protective plastic cap from the top of the INTRON A vial.
2. Clean the rubber stopper on the top of the INTRON A vial with an alcohol swab.
3. Remove the protective cap from the syringe needle and fill with air by pulling the plunger to the level that represents your dose as indicated by your doctor (Figure A).

Figure A

Hold the INTRON A vial upright without touching the cleaned top of the vial with your hands (Figure B).

Figure B

Insert the needle into the vial containing the INTRON A solution and inject the air into the vial (Figure C).

Figure C

4. Turn vial and syringe upside down in one hand. Be sure tip of needle is in the INTRON A solution. Your other hand will be free to move the plunger. Pull back on plunger slowly to draw the correct dose as prescribed by your doctor into syringe (Figure D).

Figure D

5. Remove needle from vial (Figure E) and check for air bubbles in the syringe. If you see any bubbles, tap the syringe gently and with the needle pointing up, push the plunger slowly until the bubbles disappear.

Figure E

6. Replace the needle cap. **If the solution is cold, warm syringe between hands.** Lay syringe down on a flat surface so that needle does not touch anything.

FOR SUBCUTANEOUS INJECTION

1. Selecting the Site for Injection
   - The best sites for injection are tissues with a layer of fat between skin and muscle
   - thigh
   - outer surface of the upper arm
   - abdomen, except the navel or waistline.
   - If your are exceptionally thin, use only the thigh or outer surface of the arm for injection.
   - Do not inject INTRON A solution in the same place repeatedly - change your injection site in a regular pattern.

2. Cleanse the skin where the injection is to be made with an alcohol swab. Wait for area to dry. Remove cap from needle. With one hand, pinch a 2-inch fold of loose skin.
3. With your other hand pick up syringe, and hold it as your would a pencil. Insert needle approximately 1/4 inch into the pinched skin at an angle of 45° to 90°.

After the needle is in, remove hand used to pinch skin and use it to hold syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject. Withdraw and discard needle and syringe. Prepare a new syringe and inject at a new site. (Follow steps 2 and 3.)

4. If blood does not appear in the syringe, push plunger all the way down gently.
5. Hold alcohol swab near the needle and pull needle straight out of skin. Press alcohol swab over injection site for several seconds. Do not massage injection site. If there is bleeding, cover with an adhesive bandage.
6. Use disposable syringe only once to ensure sterility of syringe and needle. Dispose of syringe and needle as directed.

You should be instructed on the proper handling and disposal of all syringes and needles, and the importance of not reusing any syringes or needles.

The container for the disposal of used needles and syringes should be supplied to you. The full container should be disposed of according to directions provided by your doctor or nurse.

7. After 2 hours, check injection site for signs of inflammation, such as redness, swelling, or tenderness; if there are any, contact your doctor or nurse.

How do I store my medication?

STORAGE OF REBETOL CAPSULES

REBETOL Capsules should be stored in the refrigerator between 2° and 8°C (36° and 46°F) or at room temperature 25°C (77°F). The capsules may be stored at temperatures between 25° and 30°C (77° and 86°F) for short periods of time.

STORAGE OF INTRON A INJECTION

INTRON A Injection should be stored in the refrigerator between 2° and 8°C (36° and 46°F), not in the freezer.

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